(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/064798 A1

(51) International Patent Classification[7]: A61K 7/48

(21) International Application Number:
PCT/BE2004/000011

(22) International Filing Date: 20 January 2004 (20.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/319,887	20 January 2003 (20.01.2003)	US
03447019.5	28 January 2003 (28.01.2003)	EP

(71) Applicant *(for all designated States except US)*: AURIGA INTERNATIONAL S.A. [BE/BE]; Chemin des Roussettes, 2, B-1410 WATERLOO (BE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: MARCHAL, Alfred [BE/BE]; Chemin des Roussettes, 2, B-1410 WATERLOO (BE).

(74) Agents: VAN MALDEREN, Joëlle et al.; OFFICE VAN MALDEREN, Place Reine Fabiola 6/1, B-1083 Brussels (BE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF A COMPOSITION COMPRISING VITAMIN K1 OXIDE OR A DERIVATIVE THEREOF FOR THE TREATMENT AND/OR THE PREVENTION OF MAMMAL DERMATOLOGICAL LESIONS

(57) Abstract: The present invention is related to the use of a composition which comprises an adequate pharmaceutical or cosmetic carrier or diluent and a sufficient amount of vitamin K1 oxide or its derivative for the treatment and/or the prevention of mammal dermatological lesions. The present invention is also related to a cosmetic composition which comprises an adequate cosmetic carrier, phospholipids and vitamin K1 oxide or its derivative.

WO 2004/064798 A1

USE OF A COMPOSITION COMPRISING VITAMIN K1 OXIDE OR A DERIVATIVE THEREOF FOR THE TREATMENT AND/OR THE PREVENTION OF MAMMAL DERMATOLOGICAL LESIONS

Field of the invention

[0001] The present invention is related to the use of a composition comprising vitamin K1 oxide or a derivative thereof for the treatment and/or the prevention of mammal dermatological lesions and to the cosmetic composition comprising vitamin K1 oxide.

Background of the invention and state of the art

[0002] Vitamin K1 (phylloquinone) is needed for proper bone formation and blood clotting, in both cases by helping the body transport calcium. Vitamin K (2-methyl 3-phytyl-1, 4-naphtoquinone) and its derivative have already been used in pharmaceutical or cosmetic compositions for their various anti-inflammatory or dermatological applications.

[0003] However, the incorporation of vitamin K1 in a cosmetic composition is unstable in certain conditions when exposed to light and UV light and could modify the colour of cream and other vehicles of cosmetic compositions.

[0004] The document US-5 510 391 describes a method for treating blood vessel disorders of the skin using vitamin K. Such disorders include actinic and iatrogenic purpura, lentigines, telangiectasias of the face, spider angiomas and spider veins of the face.

[0005] The document JP-05320039 describes a cosmetic composition comprising vitamin K1 oxide without specification of any use.

[0006] The document WO94/00135 describes the use of a pharmaceutical composition in the treatment of symptoms of chronic inflammatory disorders, said composition comprising at least two pharmaceutically active agents whose combination produces an anti-inflammatory and analgesic effect. Said document also describes that the safety and effectiveness of the product may be optimised by co-administration of vitamins and derivatives thereof. Among the mentioned vitamins are vitamin K1 and vitamin K1 oxide.

[0007] The document GB-744 376 describes a stable oily vitamin emulsion comprising an oily vitamin and lecithin dispersed in water. The vitamins could be vitamin A, D, E, K1 or vitamin K1 oxide. Said document also describes that vitamin K1 oxide emulsion is a colourless oil, somewhat more stable than vitamin K1, but having the same physiological activity as vitamin K1 and resulting in a stable emulsion which is not affected by heating at a temperature of 120° C for two hours period.

[0008] The document US-3 070 499 describes a parenteral aqueous solution of fat soluble vitamin wherein the fat soluble substance is vitamin K1 oxide which finds application in nutrition for the prevention and the treatment of certain well known diseases.

Aims of the invention

[0009] A first aim of the present invention is to propose a new composition which finds advantageous applications in the treatment of various mammal dermatological lesions, especially human dermatological lesions, and more especially lesions which affect the face,

but which does not present the drawbacks of the state of the art.

[0010] Another aim of the present invention is to provide such composition which is more stable and which does not present the yellow colour of cream and vehicles already used in the state of the art and which therefore does not render the clothes of the consumer dirty.

[0011] A further aim of the present invention is to provide a composition which is not sensitive to light or UV-radiation and which therefore decreases or eliminates side effects such as consumer skin sensitivity or allergy following sun exposure.

[0012] A last aim of the present invention is to provide a composition having a similar or an improved activity (including an enhanced penetration through the skin and an excellent moisture-binding capacity) in view of the known composition of the state of the art.

Summary of the invention

[0013] A first aspect of the present invention is related to the use of a composition comprising vitamin K1 oxide or a derivative thereof and an adequate carrier for the treatment and/or the prevention of mammal (including human) dermatological lesions, selected from the group consisting of bruises (possibly associated with cosmetic surgery), vascular disorders of the skin such as small broken vessels, spider veins, varicoses, blotches on the face, any purpura on the face, body and legs (including actinic purpura and post laser skin treatment purpura), irritation of the skin following chemical peel, Shambourg's disease and a mixture thereof.

[0014] Advantageously, the use of the composition according to the invention also presents other advantageous associated therapeutical effects when applied upon

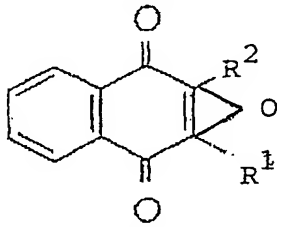
dermatological lesions, such as topical anti-inflammatory effects upon the human skin.

[0015] Preferably, the composition used according to the invention is either in the form of a pharmaceutical composition or a cosmetic composition comprising an adequate pharmaceutical or cosmetic carrier or diluent.

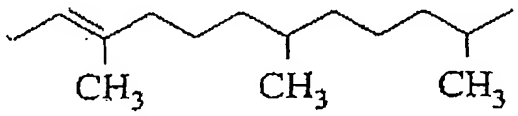
[0016] Advantageously, the cosmetic composition further comprises a sufficient amount of a penetrating agent such as phospholipids, preferably said penetrating agent is in the form of nanosomes, described hereafter.

[0017] Examples of a cosmetic composition could be in the form of a cream, a gel, a lotion and/or a liquid.

[0018] The vitamin K1 oxide present in the composition has the following formula (I) derivative:



wherein R1 is an alkyl group, preferably an alkyl chain comprising between 3 and 20 carbons, preferably an alkyl chain of 12 carbons, possibly branched, more preferably of fomula (II).



and wherein R2 is H or an alkyl group, preferably a ethyl or a methyl group.

[0019] Advantageously, the vitamin present in the composition has the formula I wherein R1 is of formula II and R2 is a methyl group (vitamin K1 oxyde).

[0020] Advantageously, in the composition according to the invention, the compound of the invention (vitamin K1

oxide or its derivative) is present in nano-sized lipidic particles (hereafter called nanosomes), preferably lipidic particles having a diameter comprised between about 50 and about 400 nanometers, more preferably between about 100 and about 350 nanometers, between about 120 and about 300 nanometers, between about 155 nanometers and about 200 nanometers, more preferably about 180 nanometers (± 30 nanometers).

[0021] The stability of the lipidic nanosome is obtained with particles having a suitable dimension of about 180 nanometers and more than 80% (preferably all) of the nanosomes of the composition should reach the same size of about 180 nanometers. If it happens that a difference in such size exceeds 30%, then a fusion process will occur meaning the formation of greater nanosomes that will become instable and further will destroyed themselves by breaking. It results in a possible dispersion of the compound (vitamin K1 oxide or its derivative) and the lipidic membrane and loose of the nanosome advantages.

[0022] Advantageously, the extend structure of the nanosome has the same physico-chemical properties that the cell membrane and therefore, the nanosome is able to penetrate easily and quickly the skin and improve the cosmetic and therapeutic properties of the compound (vitamin K1 oxide or its derivative). Furthermore, the integration of the compound (vitamin K1 oxide or its derivative) in nanosomes will enhance therapeutical and cosmetical efficacy while using less substance.

[0023] The nanosomes are made of single or multi-lipidic layers of phospholipids, preferably of phosphatidylcholine. Preferably, the nanosomes are single lipidic monolayers of phospholipids, preferably of phosphatidylcholine.

[0024] In the composition according to the invention, the compound (vitamin K1 oxide or its derivative) is present in a sufficient amount to treat or reduce the effect of the above-mentioned dermatological lesions. Preferably, said sufficient amount is comprised between 0.5% wt and about 10% wt of the total composition, preferably about 5% wt of the total composition (the total % wt of the composition being 100%).

[0025] The composition according to the invention advantageously comprises other efficient cosmetic or pharmaceutical compounds, such as other vitamins (which could be present in nanosomes, preferably having the same size as the ones which include vitamin K1 oxide or its derivative). Preferred vitamins are vitamin A, vitamin C and vitamin E which present advantageously a synergic activity with vitamin K1 oxide or its derivative. Vitamins C and E are able to maintain iron under a bivalent form (ferrous) avoiding transformation to trivalent form (ferric).

[0026] In the composition according to the invention, the vitamin A (pure retinol) could be in the form of ester of vitamin A which is more stable for a cosmetic use. With the use of ester derivatives, the efficacy is reduced.

[0027] Furthermore, when using in eyes area, a possible irritating side effect of retinol could be obtained, especially when the cosmetic composition is used for a long period of time. Therefore, retinol is preferably introduced into polymer system of micro particles that deliver the retinol slowly through the stratum corneum, only when the product is applied directly on the skin. The polymer sphere will remain on the surface of the skin. In order to reduce a possible soft light effect with barium sulphate, mica and titanium dioxide (this mineral can not

penetrate the skin and shows a change in the common light with a dulled effect), the concentration of said compound could be reduce in the cosmetic composition according to the invention, especially if the treatment should take several months.

[0028] Other active ingredients are ingredients which improve the vitamin activity, preferably said compounds are selected from the group consisting of the following elements with the following preferred (wt) %: phytonadione (about 0.5 to about 2%), tocopheryl acetate (about 1%), ascorbic palmitate (about 0.5%), retinyl palmitate (about 0.5%) and tocopherol (about 0.2%).

[0029] Other advantageous compounds comprised in the composition (a cosmetic composition of the invention) are: aqua (solvent), retinol, propylene glycol (moistening element), triethanolamin (neutralizing element), lecithin (improves hydratation), carbomer (thickening element), ethoxydiglycol (penetration agent), some specific lipids, such as phospholipids (penetration agents), EDTA (complexing agent), C12-C15 alkyl benzoate, caprylic capric triglycerides, parafinum liquidum, cyclomethicone, glycerine, sodium PCA, mica, barium sulfate, titanium dioxide, polysorbate 20, acrylate copolymer, phenoxyethanol, acrylate C10-C30, alkyl crosspolymer, propyl paraben, menthyl paraben, alcohol (conservative), propylene glycol (moistening agent), BHT or BHA (antioxidants), ...

[0030] The phospholipids used in the present invention improve the skin penetration of vitamins, especially vitamin K1 oxide or its derivative and vitamin A.

[0031] The present invention will be described in more details in the following examples, presented as a

non-limited illustration of preferred embodiment of the present invention.

Example 1: Protocol for bruises

[0032] For the purpose of the study, three compositions (cream cosmetic compositions) have been used in various vehicles with different concentrations in vitamin K1 and vitamin K1 oxide. The study was conducted in double blind on 12 human volunteers (six males and six females). The purpose of the study was to show a better or at least a similar activity of vitamin K1 oxide versus vitamin K1 in resolution of bruises.

[0033] The 12 human volunteers previously received information on the goal and the course of the trial. Four ecchymoses have been induced on each patient (2 on each forearms) and the efficacy of each cream cosmetic composition has been evaluated by observation of time reduction of each ecchymosis. Each patient was examined every day and pictures have been taken at the same time. No other cream was applied and the patients were not allowed to take any other medication (no aspirin, no anti-inflammatory active compound). The creams were applied twice a day.

Materials and method

The table 1 presents 4 different creams and their contents.

Table 1

Creams	
cream 1	5% free vitamin K1 cream
cream 2	2% vitamin K1 gel (nanosome particles)
cream 3	5% vitamin K1 oxide cream
cream 4	No treatment as witness

[0034] The following quantitative results in days of reduction of bruises are presented in the following table 2 and show the advantageous effects of vitamin K1 oxide compared to vitamin K1 upon different patients.

Table 2

Cream 1	Cream 2	Cream 3	Cream 4
Patient	5% Vitamin K1	2% Vitamin K1 nanosome particles	5% Vitamin K1 Oxide	No treatment
A1	11	9	11	10
A2	11	8	10	11
A3	13	10	10	13
A4	10	11	13	13
A5	11	11	9	14
A6	13	11	11	13
B1	12	9	10	12
B2	12	11	11	13
B3	13	11	10	12
B4	12	10	10	13
B5	12	12	10	13
B6	12	11	9	11
Total	142	124	124	148
Mean	11,83	10,33	10,33	12,33

Example 2: Protocol for spider veins

[0035] The same study was performed on 10 human patients presenting spider veins or small broken blood vessels on legs and face.

[0036] The treatment was done during four weeks with two applications of the creams per day.

[0037] The group vitamin Oxide shows the best results compared to other formulation comprising vitamin K1.

[0038] The composition (a cosmetic composition according to the invention) may be applied thinly twice a day, morning and evening, after cleansing of the skin; gently massage into skin and till the gel is absorbed, is preferred.

[0039] The composition according to the invention is recommended for use for 10 to 15 days as preparatory skin care before and after surgical and medical cosmetic procedure.

[0040] The composition according to the invention should preferably be applied before all other beauty or cosmetic skin care products and can be used as a base for those preparations; said composition should not be applied directly upon wounds, mucus areas or eyes due to some hyper-sensitivity.

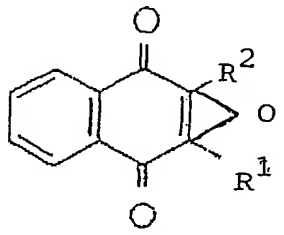
[0041] The improved stability of vitamin K1 oxide compared to vitamin K1, reduces also unexpectedly the side effects of a cosmetic composition. The inventors have observed that in presence of light (and possibly improved with the addition of vitamin A), vitamin K1 is transformed into Menadione (vitamin K3) and 1.4.Naphtoquinone that induces allergic side effects. Such transformation of vitamin K1 oxide is not observed in the presence of light and these side effects are not present when the cosmetic composition according to the invention is applied upon mammal skin.

[0042] Furthermore, contrary to vitamin K1, the mixing of vitamin K1 oxide and retinol (or retinol palmitate) does not allow the formation of chromophoric group.

[0043] The introduction of active ingredients, especially vitamin K1 oxide and its derivative, in nanosomes improves advantageously penetration and absorption of vitamins, reduces the concentration of vitamins required and provides a system release of vitamins for about 12 hours and therefore reduces the cost of the composition compared to the compositions of the state of the art.

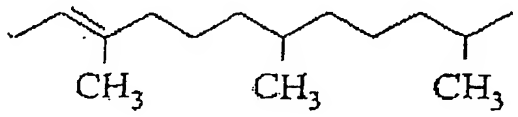
CLAIMS

1. Use of a composition comprising an adequate pharmaceutical or cosmetic carrier (or diluent) and a sufficient amount of a compound formula I



wherein R1 is an alkyl group and wherein R2 is H or an alkyl group.

2. The use of claim 1, wherein R1 is an alkyl chain of formula II



wherein R2 is a methyl.

3. The use of claim 1 or 2, wherein the compound is present in nano-sized lipidic particles, comprised between about 50 and about 400 nanometers in diameter.

4. The use of claim 3, wherein the nano-sized lipidic particles have a diameter of about 180 nanometer.

5. The use of claim 3 or 4, wherein the nano-sized lipidic particles are made of phospholipid layers.

6. The use of claim 1 to 3, wherein the composition is a cosmetic composition comprising a sufficient amount of the compound and an adequate cosmetic carrier.

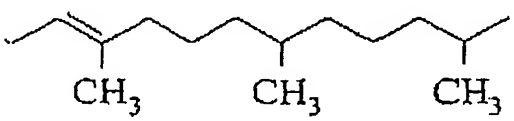
7. The use of claim 6, wherein the sufficient amount of the compound is comprised between about 0.5% wt and about 10% wt of the composition.

8. The use of claim 6 or 7, wherein the cosmetic composition is in the form of a cream, a gel, a lotion or a liquid.

9. The use according to any of the preceding claims 6 to 8, wherein the composition further comprised other vitamins, preferably vitamins selected from the group consisting of vitamin A, vitamin C, vitamin E or a mixture thereof.

10. A cosmetic composition which comprises an adequate cosmetic carrier and phospholipids and a compound of formula I for the treatment and/or the prevention of mammal dermatological lesions, selected from the group consisting of bruises, vascular disorder on the skin, spider veins, varicoses, blotches on the face, purpura on the face, body or legs, irritation following use of chemical peel, Shambourg's disease or a mixture thereof, wherein R1 is an alkyl group and wherein R2 is H or an alkyl group.

11. The cosmetic composition of claim 10, wherein the compound of formula I, R1 is a alkyl chain of formula II



wherein R2 is a methyl.

12. The cosmetic composition according to claim 10 or 11, wherein the compound is present in nano-sized lipidic particles, comprised between about 50 and about 400 nanometers in diameter.

13. The cosmetic composition according to claim 12, wherein the compound is present in nano-sized lipidic particles of about 180 nanometer in diameter.

14. The composition of claim 12 or 13, wherein the nano-sized lipidic particles are made of a phospholipid layer.

15. The cosmetic composition according to the claims 10 to 14, wherein the compound is present in a percentage in the composition comprised between about 0.5% wt to about 10% wt of the composition.

16. The cosmetic composition according to any of the claims 10 to 15 which is in the form of a cream, a gel, a lotion or a liquid.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/BE2004/000011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199402 Derwent Publications Ltd., London, GB; Class B05, AN 1994-012183 XP002244372 & JP 05 320039 A (TAIYO KAGAKU KK) 3 December 1993 (1993-12-03) abstract	1,2,6-8
X	WO 94/00135 A (SHAPIRO HOWARD K) 6 January 1994 (1994-01-06) page 57, paragraph 2; claims 1,14,18	1,2,8
X	GB 744 376 A (MERCK & CO INC) 8 February 1956 (1956-02-08) claims 1,2; example 2	1-8, 10-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2004	02/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Yon, J-M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Interg ınal Application No
PCT/BE2004/000011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 070 499 A (MACEK THOMAS J ET AL) 25 December 1962 (1962-12-25) column 2, line 22 - line 24; claims 1,6; example 2	1,2,7,8
A	WO 97/39746 A (ADVANCED POLYMER SYSTEMS INC) 30 October 1997 (1997-10-30) claims 1,7,13	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/BE2004/000011

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
JP 5320039	A	03-12-1993	NONE		
WO 9400135	A	06-01-1994	AT	214608 T	15-04-2002
			AU	674330 B2	19-12-1996
			AU	4655393 A	24-01-1994
			CA	2120367 A1	06-01-1994
			DE	69331727 D1	25-04-2002
			EP	0604641 A1	06-07-1994
			WO	9400135 A1	06-01-1994
			US	6444221 B1	03-09-2002
GB 744376	A	08-02-1956	NONE		
US 3070499	A	25-12-1962	GB	946086 A	08-01-1964
WO 9739746	A	30-10-1997	AU	2804297 A	12-11-1997
			WO	9739746 A1	30-10-1997